REMARKS

A. Status of the Claims

Claims 1-4, 9 and 10 are pending in the application and stand rejected under 35 U.S.C. §102 as anticipated by Kufe *et al.* Claims 1-4, 9 and 10 also stand rejected as obvious under 35 U.S.C. §103 over Dobie *et al.* in view of Tuschl *et al.* The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

B. Rejections Under 35 U.S.C. §102

Claims 1-4, 9 and 10 remain rejected as anticipated by Kufe *et al.* Applicants traverse. Documents adding Dr. Steven Weitman as an inventor to the instant application are submitted herewith. Thus, reconsideration and withdrawal of the rejection on the grounds that Kufe *et al.* is not §102(e) prior art "by another" is respectfully requested.

C. Rejection Under 35 U.S.C. §103

Claims 1-4, 9 and 10 remain rejected as obvious over Dobie *et al.* in view of Tuschl *et al.* According to the examiner, it would have been obvious to substitute the antisense molecule of Dobie *et al.* with the siRNA of Tuschl *et al.*, thereby arriving at the presently claimed invention Applicants traverse.

1. Lack of Motivation

Dobie focuses on antisense oligomeric compounds, particularly antisense oligonucleotides, to downregulate MUC1 expression, and use of these compounds in the treatment of diseases associated with expression of MUC1. See, *e.g.*, title, abstract, and col. 5, lines 57-61. Dobie teaches antisense as being "preferred" for its methods, and focuses almost exclusively on antisense technology. See Dobie, col. 6, lines 21-23. Dobie also teaches numerous antisense oligonucleotides that inhibit expression of the MUC1 gene. *See*, *e.g.*, Table

1, col. 48–51. It teaches that antisense provides "specificity and sensitivity" which can be "harnessed by those of skill in the art for therapeutic uses." Col. 9, lines 38-39.

While Dobie may teach an antisense oligonucleotide that hybridizes to positions 585-604 of SEQ ID NO:10, it does not provide any teaching or suggestion to apply RNA interference to downregulate MUC1, or to use of any double-stranded RNA to downregulate MUC1. The The examiner argues that Tuschl provides motivation to one of ordinary skill in the art to substitute RNA interference with the antisense technology of Dobie. Applicant disagrees.

First, though siRNA is stated to be a powerful tool, and in the system utilized in Tuschl is said to work at lower levels than antisense, there is no guarantee that such will work the ***same*** way in ***all*** systems. It is critical to note that the Tuschl data are in *D. melanogaster* – not even a mammalian system, and certainly not in human cells. Thus, the examiner's sweeping statement that Tuschl obviates the use of any siRNA for use in any mammalian system for any purpose is simply not supported.

For each of the foregoing reasons, one of ordinary skill in the art would not have been motivated to substitute the antisense compounds of Dobie with the double-stranded RNA of Tuschl. Further, even if the references were so combined, there was no likelihood that a successful inhibition or MUC-1 would have resulted, as explained further, below.

2. Lack of Likelihood of Success

Also, one of ordinary skill in the art would not assume that a successful antisense approach could be duplicated with RNA interference. Antisense technology, as disclosed by Dobie, relies on the hybridization of a nucleic acid – usually DNA and always single-stranded – to a target sequence – almost always an RNA – to inhibit translation. RNAi works in a completely different fashion – double-stranded RNA is provided to a cell that results in cleavage of target RNA.

In the attached declaration, one of the present inventors points out differences between "interference RNA" and "antisense RNA." Citing Bumcrot *et al.* (2006), he notes that "[i]n RNAi, the target mRNA is enzymatically cleaved, leading to decreased abundance of the corresponding protein." See Bumcrot *et al.*, page 711 and FIG. 1. Further, the interfering RNA is a "double-stranded RNA." In RNA interference, long double-stranded RNA (dsRNA) is cleaved into small interfering RNA (siRNA). This mechanism is ***entirely distinct*** from gene inhibition using antisense RNA, where the antisense RNA is a single-stranded RNA molecule. Thus, antisense technology works in a ***completely*** different fashion than RNAi, and thus one would not be able to conclude, without more, that success in the former would translate to success with the latter.

In *Takeda Chemical v. Alphapharm*, the Federal Circuit held that in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." *Takeda Chem. Indus. V. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). In the instant case, the examiner has not provided any reason that would have led a chemist to modify the antisense oligonucleotide of Dobie into a double-stranded RNA complex. Double-stranded RNA complexes are structurally distinct from the single-stranded molecules of Dobie. Further, as discussed above, antisense technology, which involves single stranded molecules, works in a completely different fashion than RNA interference, which involves double-stranded RNA. Thus, there being no motivation for a chemist to modify the compounds of Dobie into the compounds of the claimed invention, there can be no *prima facie* case of obviousness.

Dr. Kufe also cites to Miyagishi *et al.* (2003). Miyagishi *et al.* compared the effects of antisense antisense oligonucleotides and siRNAs directed against the same targets in mammalian

cells. The targets were six sites in the firefly gene for luciferase. Results showed that there were significant differences in the suppressive effects at each of the target sites. See Miyagishi *et al.*, page 5, left column, and FIG. 2A and FIG. 3. As can be seen from FIG. 2A and FIG. 3, the correlation coefficient between the results for antisense ODN's and siRNA was low (0.42). In view of this evidence, a person of ordinary skill in the field, who would have been familiar with Miyagishi *et al.*, would have understood that the effects of antisense technology are not necessarily the same as the effects with RNA interference.

Therefore, one of ordinary skill in the art would not have any reasonable expectation of success that RNA interference could be successfully applied in down-regulating MUC1. In view of the foregoing, it is respectfully submitted that the claims are not obvious as argued by the examiner.

3. The Examiner's Attempted Rebuttal

In the examiner argues an number of points in disputing the arguments submitted with the previous response, and recast above in this response.

First, the examiner argues that the Kufe Declarations from a related case, despite being precisely on point and dealing with very similar references, are not relevant here. Applicants traverse, but in the interest of advancing the prosecution, the declarations have been revised and re-executed for consideration in the instant application.

Second, the examiner argues that Tuschl stands for the proposition that ***any*** gene target can be inhibited with siRNA. However, the examiner conveniently ignores that Tuschl was working in *Drosophila*, while the present claims address mammalian cells. It is not credible to equate these two bodies of work, much less argue that one can predict outcomes in the other. Moreover, it is not applicants' burden to establish the ***im***propriety of making this extrapolation,

as suggested by the examiner. Rather it is the ***examiner's*** burden to prove it is proper. Nothing of the sort has even been attempted on the record here.

Third, the examiner admits that the mechanisms of antisense and siRNA are different, but then simply dismisses this salient fact as "not on point." Why? Biological systems are inherently unpredictable, as the PTO is quite fond of reminding applicants. Here, the examiner simply states that because siRNA was a viable option, it is *ipso facto* obvious to substitute it for antisense methods. Whatever changes there might be in the post-*KSR* world of obviousness, the standard was not so altered as to make motivation a nullity.

In sum, applicants have provided sound reason to question both the very combination of references offered by the examiner, and the conclusions one could draw regarding the outcome of the combination if made. Therefore, it is again submitted that the rejection is improper and should be reconsidered and withdrawn.

D. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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Date: September 23, 2010